CLONAZEPAM - clonazepam tablet, orally disintegrating
Alembic Pharmaceuticals Limited

Clonazepam Orally Disintegrating Tablets, USP

C IV

Rx only

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

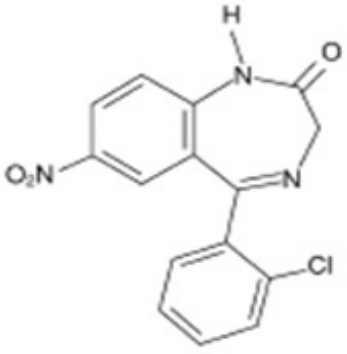
Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death (see WARNINGS and PRECAUTIONS).

- **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

DESCRIPTION

Clonazepam, USP a benzodiazepine, is available as an orally disintegrating tablet containing 0.125 mg, 0.25 mg, 0.5 mg, 1 mg or 2 mg clonazepam, USP. Each orally disintegrating tablet also contains sorbitol, aspartame, sodium lauryl sulfate, crospovidone, mannitol, colloidal silicon dioxide, talc and magnesium stearate.

Chemically, clonazepam, USP is 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one. It is a light yellow powder. It has a molecular weight of 315.72 and the following structural formula:



CLINICAL PHARMACOLOGY

Pharmacodynamics: The precise mechanism by which clonazepam exerts its antiseizure and antipanic effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system.

Convulsions produced in rodents by pentylenetetrazol or, to a lesser extent, electrical stimulation are antagonized, as are convulsions produced by photic stimulation in susceptible baboons. A taming effect in aggressive primates, muscle weakness and hypnosis are also produced. In humans, clonazepam is capable of suppressing the spike and wave discharge in absence seizures (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in minor motor seizures.

Pharmacokinetics: Clonazepam is rapidly and completely absorbed after oral administration. The absolute bioavailability of clonazepam is about 90%. Maximum plasma concentrations of clonazepam are reached within 1 to 4 hours after oral administration. Clonazepam is approximately 85% bound to plasma proteins. Clonazepam is highly metabolized, with less than 2% unchanged clonazepam being excreted in the urine. Biotransformation occurs mainly by reduction of the 7-nitro group to the 4-amino derivative. This derivative can be acetylated, hydroxylated and glucuronidated. Cytochrome P-450 including CYP3A, may play an important role in clonazepam reduction and oxidation. The elimination half-life of clonazepam is typically 30 to 40 hours. Clonazepam pharmacokinetics are dose-independent throughout the dosing range. There is no evidence that clonazepam induces its own metabolism or that of other drugs in humans.

Pharmacokinetics in Demographic Subpopulations and in Disease States: Controlled studies examining the influence of gender and age on clonazepam pharmacokinetics have not been conducted, nor have the effects of renal or liver disease on clonazepam pharmacokinetics been studied. Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Thus, caution should be exercised when administering clonazepam to these patients.

Clinical Trials: *Panic Disorder:* The effectiveness of clonazepam orally disintegrating tablets in the treatment of panic disorder was demonstrated in two double-blind, placebo-controlled studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IIIR) with or without agoraphobia. In these studies, clonazepam orally disintegrating tablets was shown to be significantly more effective than placebo in treating panic disorder on change from baseline in panic attack frequency, the Clinician's Global Impression Severity of Illness Score and the Clinician's Global Impression Improvement Score.

Study 1 was a 9-week, fixed-dose study involving clonazepam orally disintegrating tablets doses of 0.5, 1, 2, 3 or 4 mg/day or placebo. This study was conducted in four phases: a 1-week placebo lead-in, a 3-week upward titration, a 6-week fixed dose and a 7-week discontinuance phase. A significant difference from placebo was observed consistently only for the 1 mg/day group. The difference between the 1 mg dose group and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 74% of patients receiving clonazepam 1 mg/day were free of full panic attacks, compared to 56% of placebo-treated patients.

Study 2 was a 6-week, flexible-dose study involving clonazepam orally disintegrating tablets in a dose range of 0.5 to 4 mg/day or placebo. This study was conducted in three phases: a 1-week placebo lead-in, a 6-week optimal-dose and a 6-week discontinuance phase. The mean clonazepam dose during the optimal dosing period was 2.3 mg/day. The difference between clonazepam orally disintegrating tablets and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 62% of patients receiving clonazepam were free of full panic attacks, compared to 37% of placebo-treated patients.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of race or gender.

INDICATIONS AND USAGE

Seizure Disorders: Clonazepam orally disintegrating tablet is useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. In patients with absence seizures (petit mal) who have failed to respond to succinimides, clonazepam orally disintegrating tablets may be useful.

In some studies, up to 30% of patients have shown a loss of anticonvulsant activity, often within 3 months of administration. In some cases, dosage adjustment may reestablish efficacy.

Panic Disorder: Clonazepam orally disintegrating tablet is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-V. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of clonazepam orally disintegrating tablets was established in two 6- to 9-week trials in panic disorder patients whose diagnoses corresponded to the DSM-IIIR category of panic disorder (see CLINICAL PHARMACOLOGY: *Clinical Trials*).

Panic disorder (DSM-V) is characterized by recurrent unexpected panic attacks, ie, a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The effectiveness of clonazepam orally disintegrating tablets in long-term use, that is, for more than 9 weeks, has not been systematically studied in controlled clinical trials. The physician who elects to use clonazepam orally disintegrating tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Clonazepam orally disintegrating tablets are contraindicated in patients with the following conditions:

- History of sensitivity to benzodiazepines
- Clinical or biochemical evidence of significant liver disease
- Acute narrow angle glaucoma (it may be used in patients with open angle glaucoma who are receiving appropriate therapy).

WARNINGS

Risks from Concomitant Use With Opioids: Concomitant use of benzodiazepines, including clonazepam orally disintegrating tablets, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe clonazepam orally disintegrating tablets concomitantly with opioids, prescribe the lowest

effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when clonazepam orally disintegrating tablet is used with opioids (see PRECAUTIONS: *Information for Patients* and PRECAUTIONS: *Drug Interactions*).

Interference With Cognitive and Motor Performance: Since clonazepam orally disintegrating tablets produces CNS depression, patients receiving this drug should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle. They should also be warned about the concomitant use of alcohol or other CNS-depressant drugs during clonazepam orally disintegrating tablets therapy (see PRECAUTIONS: *Drug Interactions* and *Information for Patients*).

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including clonazepam orally disintegrating tablets, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono-and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43% compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1	3.4	3.5	2.4

Psychiatric	5.7	8.5	1.5	2.9
Other	1	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing clonazepam orally disintegrating tablets or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Pregnancy Risks: Data from several sources raise concerns about the use of clonazepam orally disintegrating tablets during pregnancy.

Animal Findings: In three studies in which clonazepam orally disintegrating tablets was administered orally to pregnant rabbits at doses of 0.2, 1, 5 or 10 mg/kg/day (low dose approximately 0.2 times the maximum recommended human dose of 20 mg/day for seizure disorders and equivalent to the maximum dose of 4 mg/day for panic disorder, on a mg/m^2 basis) during the period of organogenesis, a similar pattern of malformations (cleft palate, open eyelid, fused sternebrae and limb defects) was observed in a low, non-dose-related incidence in exposed litters from all dosage groups. Reductions in maternal weight gain occurred at dosages of 5 mg/kg/day or greater and reduction in embryo-fetal growth occurred in one study at a dosage of 10 mg/kg/day. No adverse maternal or embryo-fetal effects were observed in mice and rats following administration during organogenesis of oral doses up to 15 mg/kg/day or 40 mg/kg/day, respectively (4 and 20 times the maximum recommended human dose of 20 mg/day for seizure disorders and 20 and 100 times the maximum dose of 4 mg/day for panic disorder, respectively, on a mg/m^2 basis).

General Concerns and Considerations About Anticonvulsants: Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

In children of women treated with drugs for epilepsy, reports suggesting an elevated incidence of birth defects cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors (eg, genetic factors or the epileptic condition itself) may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should

not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy; however, it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus.

General Concerns About Benzodiazepines: An increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested in several studies.

There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, children born to mothers receiving benzodiazepines late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.

Advice Regarding the Use of Clonazepam Orally Disintegrating Tablets in Women of Childbearing Potential: In general, the use of clonazepam orally disintegrating tablets in women of childbearing potential, and more specifically during known pregnancy, should be considered only when the clinical situation warrants the risk to the fetus.

The specific considerations addressed above regarding the use of anticonvulsants for epilepsy in women of childbearing potential should be weighed in treating or counseling these women.

Because of experience with other members of the benzodiazepine class, clonazepam orally disintegrating tablet is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency in the treatment of panic disorder, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant, they should communicate with their physician about the desirability of discontinuing the drug.

Withdrawal Symptoms: Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

PRECAUTIONS

General:

Worsening of Seizures: When used in patients in whom several different types of seizure disorders coexist, clonazepam orally disintegrating tablets may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). This may require the addition of appropriate anticonvulsants or an increase in their dosages. The concomitant use of valproic acid and clonazepam orally disintegrating tablets may produce absence status.

Laboratory Testing During Long-Term Therapy: Periodic blood counts and liver function tests are advisable during long-term therapy with clonazepam orally disintegrating tablets.

Risks of Abrupt Withdrawal: The abrupt withdrawal of clonazepam orally disintegrating tablets, particularly in those patients on long-term, high-dose therapy, may precipitate status epilepticus. Therefore, when discontinuing clonazepam orally disintegrating tablet gradual withdrawal is essential. While clonazepam orally disintegrating tablet is being gradually withdrawn, the simultaneous substitution of another anticonvulsant may be indicated.

Caution in Renally Impaired Patients: Metabolites of clonazepam orally disintegrating tablets are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

Hypersalivation: Clonazepam orally disintegrating tablets may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions.

Respiratory Compromise: Clonazepam orally disintegrating tablets should be used with caution in patients with compromised respiratory function.

Porphyria: Clonazepam orally disintegrating tablets may have a porphyrogenic effect and should be used with care in patients with porphyria.

Information for Patients:

A clonazepam orally disintegrating tablets Medication Guide must be given to the patient each time clonazepam orally disintegrating tablets are dispensed, as required by law. Patients should be instructed to take clonazepam orally disintegrating tablets only as prescribed. Physicians are advised to discuss the following issues with patients for whom they prescribe clonazepam orally disintegrating tablets:

Risks from Concomitant Use With Opioids: Inform patients and caregivers that potentially fatal additive effects may occur if clonazepam orally disintegrating tablet is used with opioids and not to use such drugs concomitantly unless supervised by a health care provider (see WARNINGS: *Risks from Concomitant Use With Opioids* and PRECAUTIONS: *Drug Interactions*).

Dose Changes: To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

Interference With Cognitive and Motor Performance: Because benzodiazepines have the potential to impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that clonazepam orally disintegrating tablets therapy does not affect them adversely.

Suicidal Thinking and Behavior: Patients, their caregivers, and families should be counseled that AEDs, including clonazepam orally disintegrating tablets, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to

become pregnant during therapy with clonazepam orally disintegrating tablets (see WARNINGS: *Pregnancy Risks*). Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see PRECAUTIONS: *Pregnancy*).

Nursing: Patients should be advised not to breastfeed an infant if they are taking clonazepam orally disintegrating tablets.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking clonazepam orally disintegrating tablets.
Phenylketonurics: Patients should be informed that clonazepam orally disintegrating tablets contain phenylalanine (a component of aspartame). Each orally disintegrating tablet contains 0.56 mg phenylalanine.

Drug Interactions:

Effect of Concomitant Use of Benzodiazepines and Opioids: The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABAA sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Effect of Clonazepam on the Pharmacokinetics of Other Drugs: Clonazepam does not appear to alter the pharmacokinetics of phenytoin, carbamazepine or phenobarbital. The effect of clonazepam on the metabolism of other drugs has not been investigated.

Effect of Other Drugs on the Pharmacokinetics of Clonazepam: Literature reports suggest that ranitidine, an agent that decreases stomach acidity, does not greatly alter clonazepam pharmacokinetics.

In a study in which the 2 mg clonazepam orally disintegrating tablet was administered with and without propantheline (an anticholinergic agent with multiple effects on the GI tract) to healthy volunteers, the AUC of clonazepam was 10% lower and the C_{max} of clonazepam was 20% lower when the orally disintegrating tablet was given with propantheline compared to when it was given alone.

Fluoxetine does not affect the pharmacokinetics of clonazepam. Cytochrome P-450 inducers, such as phenytoin, carbamazepine and phenobarbital, induce clonazepam metabolism, causing an approximately 30% decrease in plasma clonazepam levels. Although clinical studies have not been performed, based on the involvement of the cytochrome P-450 3A family in clonazepam metabolism, inhibitors of this enzyme system, notably oral antifungal agents, should be used cautiously in patients receiving clonazepam.

Pharmacodynamic Interactions: The CNS-depressant action of the benzodiazepine class of drugs may be

potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antianxiety agents, the phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenicity studies have not been conducted with clonazepam.

The data currently available are not sufficient to determine the genotoxic potential of clonazepam.

In a two-generation fertility study in which clonazepam was given orally to rats at 10 and 100 mg/kg/day (low dose approximately 5 times and 24 times the maximum recommended human dose of 20 mg/day for seizure disorder and 4 mg/day for panic disorder, respectively, on a mg/m^2 basis), there was a decrease in the number of pregnancies and in the number of offspring surviving until weaning.

Pregnancy:

Teratogenic Effects: Pregnancy Category D (see WARNINGS: *Pregnancy Risks*).

To provide information regarding the effects of in utero exposure to clonazepam orally disintegrating tablets, physicians are advised to recommend that pregnant patients taking clonazepam orally disintegrating tablets enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on this registry can also be found at the website http://www.aedpregnancyregistry.org/.

Labor and Delivery:

The effect of clonazepam orally disintegrating tablets on labor and delivery in humans has not been specifically studied; however, perinatal complications have been reported in children born to mothers who have been receiving benzodiazepines late in pregnancy, including findings suggestive of either excess benzodiazepine exposure or of withdrawal phenomena (see WARNINGS: *Pregnancy Risks*).

Nursing Mothers:

Mothers receiving clonazepam orally disintegrating tablets should not breastfeed their infants.

Pediatric Use:

Because of the possibility that adverse effects on physical or mental development could become apparent only after many years, a benefit-risk consideration of the long-term use of clonazepam orally disintegrating tablet is important in pediatric patients being treated for seizure disorder (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION).

Safety and effectiveness in pediatric patients with panic disorder below the age of 18 have not been established.

Geriatric Use:

Clinical studies of clonazepam orally disintegrating tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Metabolites of clonazepam orally disintegrating tablets are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function. Because elderly patients are more likely to have decreased hepatic and/or renal function, care should be taken in dose selection, and it may be useful to assess hepatic and/or renal function at the time of dose selection.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of clonazepam orally disintegrating tablets and observed closely.

ADVERSE REACTIONS

The adverse experiences for clonazepam orally disintegrating tablets are provided separately for patients with seizure disorders and with panic disorder.

Seizure Disorders: The most frequently occurring side effects of clonazepam orally disintegrating tablets are referable to CNS depression. Experience in treatment of seizures has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time; behavior problems have been noted in approximately 25% of patients. Others, listed by system, including those identified during postapproval use of clonazepam orally disintegrating tablets are:

Cardiovascular: Palpitations

Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema

Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, increased appetite, nausea, sore gums

Genitourinary: Dysuria, enuresis, nocturia, urinary retention

Hematopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia

Hepatic: Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatase

Musculoskeletal: Muscle weakness, pains

Miscellaneous: Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain

Neurologic: Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, ‘‘glassy-eyed’’ appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo

Psychiatric: Confusion, depression, amnesia, hallucinations, hysteria, increased libido, insomnia, psychosis (the behavior effects are more likely to occur in patients with a history of psychiatric disturbances). The following paradoxical reactions have been observed: excitability, irritability, aggressive behavior, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid

dreams

Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages

Panic Disorder: Adverse events during exposure to clonazepam orally disintegrating tablets were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, CIGY dictionary terminology has been used to classify reported adverse events, except in certain cases in which redundant terms were collapsed into more meaningful terms, as noted below.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials:

Adverse Events Associated With Discontinuation of Treatment:

Overall, the incidence of discontinuation due to adverse events was 17% in clonazepam orally disintegrating tablets compared to 9% for placebo in the combined data of two 6-to 9-week trials. The most common events (≥1%) associated with discontinuation and a dropout rate twice or greater for clonazepam orally disintegrating tablets than that of placebo included the following:

Table 2: Most Common Adverse Events (≥1%) Associated with Discontinuation of Treatment

Adverse Event	Clonazepam Orally Disintegrating Tablets (N=574)	Placebo (N=294)
Somnolence	7%	1%
Depression	4%	1%
Dizziness	1%	<1%
Nervousness	1%	0%
Ataxia	1%	0%
Intellectual Ability Reduced	1%	0%

Adverse Events Occurring at an Incidence of 1% or More Among Clonazepam Orally Disintegrating Tablets-Treated Patients:

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of panic disorder from a pool of two 6- to 9-week trials. Events reported in 1% or more of patients treated with clonazepam orally disintegrating tablets (doses ranging from 0.5 to 4 mg/day) and for which the incidence was greater than that in placebo-treated patients are included.

The prescriber should be aware that the figures in Table 3 cannot be used to predict the incidence of

side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Table 3: Treatment-Emergent Adverse Event Incidence in 6- to 9-Week Placebo-Controlled Clinical Trials*

	Clonazepam Maximum Daily Dose					
Adverse Event by Body System	**<1mg n=96 %**	**1 to <2mg n=129 %**	**2 to <3mg n=113 %**	**≥3mg n=235 %**	**All Clonazepam Orally Disintegrating Tablets Groups N=574 %**	**Placebo N=294 %**
Central & Peripheral Nervous System						
Somnolence†	26	35	50	36	37	10
Dizziness	5	5	12	8	8	4
Coordination Abnormal†	1	2	7	9	6	0
Ataxia†	2	1	8	8	5	0
Dysarthria†	0	0	4	3	2	0
Psychiatric						
Depression	7	6	8	8	7	1
Memory Disturbance	2	5	2	5	4	2
Nervousness	1	4	3	4	3	2
Intellectual Ability Reduced	0	2	4	3	2	0
Emotional Lability	0	1	2	2	1	1
Libido Decreased	0	1	3	1	1	0
Confusion	0	2	2	1	1	0
Respiratory System						
Upper Respiratory Tract Infection†	10	10	7	6	8	4
Sinusitis	4	2	8	4	4	3
Rhinitis	3	2	4	2	2	1
Coughing	2	2	4	0	2	0
Pharyngitis	1	1	3	2	2	1
Bronchitis	1	0	2	2	1	1
Gastrointestinal System						
Constipation†	0	1	5	3	2	2
Appetite Decreased	1	1	0	3	1	1
Abdominal Pain†	2	2	2	0	1	1
Body as a Whole						
Fatigue	9	6	7	7	7	4
Allergic Reaction	3	1	4	2	2	1

Musculoskeletal						
Myalgia	2	1	4	0	1	1
Resistance Mechanism Disorders						
Influenza	3	2	5	5	4	3
Urinary System						
Micturition Frequency	1	2	2	1	1	0
Urinary Tract Infection†	0	0	2	2	1	0
Vision Disorders						
Blurred Vision	1	2	3	0	1	1
Reproductive Disorders‡						
Female						
Dysmenorrhea	0	6	5	2	3	2
Colpitis	4	0	2	1	1	1
Male						
Ejaculation Delayed	0	0	2	2	1	0
Impotence	3	0	2	1	1	0

* Events reported by at least 1% of patients treated with clonazepam orally disintegrating tablets and for which the incidence was greater than that for placebo.

† Indicates that the p-value for the dose-trend test (Cochran-Mantel-Haenszel) for adverse event incidence was ≤0.1.

‡ Denominators for events in gender-specific systems are: n=240 (clonazepam), 102 (placebo) for male, and 334 (clonazepam), 192 (placebo) for female.

Commonly Observed Adverse Events:

Table 4: Incidence of Most Commonly Observed Adverse Events* in Acute Therapy in Pool of 6- to 9-Week Trials

Adverse Event	**Clonazepam (N=574)**	**Placebo (N=294)**
Somnolence	37%	10%
Depression	7%	1%
Coordination Abnormal	6%	0%
Ataxia	5%	0%

* Treatment-emergent events for which the incidence in the clonazepam patients was ≥5% and at least twice that in the placebo patients.

Treatment-Emergent Depressive Symptoms:

In the pool of two short-term placebo-controlled trials, adverse events classified under the preferred term “depression” were reported in 7% of clonazepam orally disintegrating tablets-treated patients compared to 1% of placebo-treated patients, without any clear pattern of dose relatedness. In these same

trials, adverse events classified under the preferred term “depression” were reported as leading to discontinuation in 4% of clonazepam orally disintegrating tablets-treated patients compared to 1% of placebo-treated patients. While these findings are noteworthy, Hamilton Depression Rating Scale (HAM-D) data collected in these trials revealed a larger decline in HAM-D scores in the clonazepam group than the placebo group suggesting that clonazepam-treated patients were not experiencing a worsening or emergence of clinical depression.

Other Adverse Events Observed During the Premarketing Evaluation of Clonazepam Orally Disintegrating Tablets in Panic Disorder:

Following is a list of modified CIGY terms that reflect treatment-emergent adverse events reported by patients treated with clonazepam orally disintegrating tablets at multiple doses during clinical trials. All reported events are included except those already listed in Table 3 or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and events reported only once and which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the events occurred during treatment with clonazepam orally disintegrating tablets, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency. These adverse events were reported infrequently, which is defined as occurring in 1/100 to 1/1000 patients.

Body as a Whole: weight increase, accident, weight decrease, wound, edema, fever, shivering, abrasions, ankle edema, edema foot, edema periorbital, injury, malaise, pain, cellulitis, inflammation localized

Cardiovascular Disorders: chest pain, hypotension postural

Central and Peripheral Nervous System Disorders: migraine, paresthesia, drunkenness, feeling of enuresis, paresis, tremor, burning skin, falling, head fullness, hoarseness, hyperactivity, hypoesthesia, tongue thick, twitching

Gastrointestinal System Disorders: abdominal discomfort, gastrointestinal inflammation, stomach upset, toothache, flatulence, pyrosis, saliva increased, tooth disorder, bowel movements frequent, pain pelvic, dyspepsia, hemorrhoids

Hearing and Vestibular Disorders: vertigo, otitis, earache, motion sickness

Heart Rate and Rhythm Disorders: palpitation

Metabolic and Nutritional Disorders: thirst, gout

Musculoskeletal System Disorders: back pain, fracture traumatic, sprains and strains, pain leg, pain nape, cramps muscle, cramps leg, pain ankle, pain shoulder, tendinitis, arthralgia, hypertonia, lumbago, pain feet, pain jaw, pain knee, swelling knee

Platelet, Bleeding and Clotting Disorders: bleeding dermal

Psychiatric Disorders: insomnia, organic disinhibition, anxiety, depersonalization, dreaming excessive,

libido loss, appetite increased, libido increased, reactions decreased, aggressive reaction, apathy, attention lack, excitement, feeling mad, hunger abnormal, illusion, nightmares, sleep disorder, suicide ideation, yawning

Reproductive Disorders, Female: breast pain, menstrual irregularity

Reproductive Disorders, Male: ejaculation decreased

Resistance Mechanism Disorders: infection mycotic, infection viral, infection streptococcal, herpes simplex infection, infectious mononucleosis, moniliasis

Respiratory System Disorders: sneezing excessive, asthmatic attack, dyspnea, nosebleed, pneumonia, pleurisy *Skin and Appendages Disorders:* acne flare, alopecia, xeroderma, dermatitis contact, flushing, pruritus, pustular reaction, skin burns, skin disorder

Special Senses Other, Disorders: taste loss

Urinary System Disorders: dysuria, cystitis, polyuria, urinary incontinence, bladder dysfunction, urinary retention, urinary tract bleeding, urine discoloration

Vascular (Extracardiac) Disorders: thrombophlebitis leg

Vision Disorders: eye irritation, visual disturbance, diplopia, eye twitching, styes, visual field defect, xerophthalmia

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Clonazepam is a Schedule IV controlled substance.

Physical and Psychological Dependence: Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (eg, convulsions, psychosis, hallucinations, behavioral disorder, tremor, abdominal and muscle cramps) have occurred following abrupt discontinuance of clonazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (eg, dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed (see DOSAGE AND ADMINISTRATION). Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving clonazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

Following the short-term treatment of patients with panic disorder in Studies 1 and 2 (see CLINICAL PHARMACOLOGY: *Clinical Trials*), patients were gradually withdrawn during a 7-week downward-titration (discontinuance) period. Overall, the discontinuance period was associated with good tolerability and a very modest clinical deterioration, without evidence of a significant rebound phenomenon. However, there are not sufficient data from adequate and well-controlled long-term clonazepam studies in patients with panic disorder to accurately estimate the risks of withdrawal symptoms and dependence that may be associated with such use.

OVERDOSAGE

Human Experience: Symptoms of clonazepam overdosage, like those produced by other CNS depressants, include somnolence, confusion, coma and diminished reflexes.

Overdose Management: Treatment includes monitoring of respiration, pulse and blood pressure, general supportive measures and immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of no known value.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, should be consulted prior to use.

Flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

Serious sequelae are rare unless other drugs or alcohol have been taken concomitantly.

DOSAGE AND ADMINISTRATION

Clonazepam is available as an orally disintegrating tablet. The orally disintegrating tablet should be administered as follows: After opening the carton, peel back the foil on the blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove the tablet and place it in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without water.

Seizure Disorders: *Adults:* The initial dose for adults with seizure disorders should not exceed 1.5 mg/day divided into three doses. Dosage may be increased in increments of

0.5 to 1 mg every 3 days until seizures are adequately controlled or until side effects preclude any further increase. Maintenance dosage must be individualized for each patient depending upon response. Maximum recommended daily dose is 20 mg.

The use of multiple anticonvulsants may result in an increase of depressant adverse effects. This should be considered before adding clonazepam orally disintegrating tablets to an existing anticonvulsant regimen.

Pediatric Patients: Clonazepam orally disintegrating tablets are administered orally. In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in two or three divided doses. Dosage should be increased by no more than 0.25 to 0.5 mg every third day until a daily maintenance dose of 0.1 to 0.2 mg/kg of body weight has been reached, unless seizures are controlled or side effects preclude further increase. Whenever possible, the daily dose should be divided into

three equal doses. If doses are not equally divided, the largest dose should be given before retiring.

Geriatric Patients: There is no clinical trial experience with clonazepam orally disintegrating tablets in seizure disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of clonazepam orally disintegrating tablets and observed closely (see PRECAUTIONS: *Geriatric Use*).

Panic Disorder: *Adults:* The initial dose for adults with panic disorder is 0.25 mg bid. An increase to the target dose for most patients of 1 mg/day may be made after 3 days. The recommended dose of 1 mg/day is based on the results from a fixed dose study in which the optimal effect was seen at 1 mg/day. Higher doses of 2, 3 and 4 mg/day in that study were less effective than the 1 mg/day dose and were associated with more adverse effects. Nevertheless, it is possible that some individual patients may benefit from doses of up to a maximum dose of 4 mg/day, and in those instances, the dose may be increased in increments of 0.125 to 0.25 mg bid every 3 days until panic disorder is controlled or until side effects make further increases undesired. To reduce the inconvenience of somnolence, administration of one dose at bedtime may be desirable.

Treatment should be discontinued gradually, with a decrease of 0.125 mg bid every 3 days, until the drug is completely withdrawn.

There is no body of evidence available to answer the question of how long the patient treated with clonazepam should remain on it. Therefore, the physician who elects to use clonazepam orally disintegrating tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Pediatric Patients: There is no clinical trial experience with clonazepam orally disintegrating tablets in panic disorder patients under 18 years of age.

Geriatric Patients: There is no clinical trial experience with clonazepam orally disintegrating tablets in panic disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of clonazepam orally disintegrating tablets and observed closely (see PRECAUTIONS: *Geriatric Use*).

HOW SUPPLIED

Clonazepam orally disintegrating tablets, USP are available as follows:

0.125 mg: White to off white, round, flat-faced, beveled edge tablets, debossed with ‘L 523’ on one side and plain on other side, available in:

Cartons of 60 - 10 blisters of 6 tablets each NDC 46708-364-06

0.25 mg: White to off white, round, flat-faced, beveled edge tablets, debossed with ‘L 524’ on one side and plain on other side, available in:

Cartons of 60 - 10 blisters of 6 tablets each NDC 46708-365-06

0.5 mg: White to off white, round, flat-faced, beveled edge tablets, debossed with ‘L 525’ on one side and plain on other side, available in:

Cartons of 60 - 10 blisters of 6 tablets each NDC 46708-366-06

1 mg: White to off white, round, flat-faced, beveled edge tablets, debossed with ‘L 526’ on one side and plain on other side, available in:

Cartons of 60 - 10 blisters of 6 tablets each NDC 46708-367-06

2 mg: White to off white, round, flat-faced, beveled edge tablets, debossed with ‘L 527’ on one side and plain on other side, available in:

Cartons of 60 - 10 blisters of 6 tablets each NDC 46708-368-06

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured by:
Alembic Pharmaceuticals Limited
(Formulation Division),
Village Panelav, P. O. Tajpura,
Near Baska, Taluka-Halol,
Panchmahal 389350, Gujarat, India.

Revised: 12/2018

MEDICATION GUIDE

Clonazepam (kloe NAZ e pam)

Orally Disintegrating Tablets, USP C-IV

What is the most important information I should know about clonazepam orally disintegrating tablets?

· **Do not stop taking clonazepam orally disintegrating tablets without first talking to your healthcare provider.** Stopping clonazepam orally disintegrating tablets suddenly can cause serious side effects.

· **Clonazepam orally disintegrating tablet is a benzodiazepine medicine. Benzodiazepines can cause severe drowsiness, breathing problems (respiratory depression), coma, and death when taken with opioid medicines.**

· **Clonazepam orally disintegrating tablets can make you sleepy or dizzy and can slow your thinking and motor skills. This may get better over time.**

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how clonazepam orally disintegrating tablets affects you.
- Clonazepam orally disintegrating tablets may cause problems with your coordination, especially when you are walking or picking things up.

· **Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking clonazepam orally disintegrating tablets until you talk to your healthcare provider.** When taken with alcohol or drugs that cause sleepiness or dizziness, clonazepam orally disintegrating tablets may make

your sleepiness or dizziness worse.

· **Like other antiepileptic drugs, clonazepam orally disintegrating tablets may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

· thoughts about suicide or dying	· attempts to commit suicide	· new or worse depression
· new or worse anxiety	· feeling agitated or restless	· panic attacks
· trouble sleeping (insomnia)	· new or worse irritability	· acting aggressive, being angry, or violent
· acting on dangerous impulses	· an extreme increase in activity and talking (mania)	· other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

· Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.

· Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms. Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

· **Do not stop clonazepam orally disintegrating tablets without first talking to a healthcare provider.**

- Stopping clonazepam orally disintegrating tablets suddenly can cause serious problems. Stopping clonazepam orally disintegrating tablets suddenly can cause seizures that will not stop (status epilepticus).

· **Clonazepam orally disintegrating tablets may harm your unborn or developing baby.**

- If you take clonazepam orally disintegrating tablets during pregnancy, your baby is at risk for serious birth defects. These defects can happen as early as in the first month of pregnancy, even before you know you are pregnant. Birth defects may occur even in children born to women who are not taking any medicines and do not have other risk factors.
- Children born to mothers receiving benzodiazepine medications (including clonazepam orally disintegrating tablets) late in pregnancy may be at some risk of experiencing breathing problems, feeding problems, hypothermia, and withdrawal symptoms.
- Tell your healthcare provider right away if you become pregnant while taking clonazepam orally disintegrating tablets. You and your healthcare provider should decide if you will take clonazepam orally disintegrating tablets while you are pregnant.
- If you become pregnant while taking clonazepam orally disintegrating tablets, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can register by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- Clonazepam can pass into breast milk. Talk to your healthcare provider about the best way to feed

your baby if you take clonazepam orally disintegrating tablets. You and your healthcare provider should decide if you will take clonazepam orally disintegrating tablets or breast feed. You should not do both.

· **Clonazepam orally disintegrating tablets can cause abuse and dependence.**

- Do not stop taking clonazepam orally disintegrating tablets all of a sudden. Stopping clonazepam orally disintegrating tablets suddenly can cause seizures that do not stop, hearing or seeing things that are not there (hallucinations), shaking, and stomach and muscle cramps.
- Talk to your healthcare provider about slowly stopping clonazepam orally disintegrating tablets to avoid withdrawal symptoms.
- Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.

· **Clonazepam orally disintegrating tablet is a federal controlled substance (C-IV) because it can be abused or lead to dependence**. Keep clonazepam orally disintegrating tablets in a safe place to prevent misuse and abuse. Selling or giving away clonazepam orally disintegrating tablets may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.

What is clonazepam orally disintegrating tablet?

Clonazepam orally disintegrating tablet is a prescription medicine used alone or with other medicines to treat:

· certain types of seizure disorders (epilepsy) in adults and children

· panic disorder with or without fear of open spaces (agoraphobia) in adults

It is not known if clonazepam orally disintegrating tablet is safe or effective in treating panic disorder in children younger than 18 years old.

Do not take clonazepam orally disintegrating tablet if you:

· are allergic to benzodiazepines

· have significant liver disease

· have an eye disease called acute narrow angle glaucoma

Ask your healthcare provider if you are not sure if you have any of the problems listed above.

Before you take clonazepam orally disintegrating tablets, tell your healthcare provider about all your medical conditions, including if you:

· have liver or kidney problems

· have lung problems (respiratory disease)

· have or have had depression, mood problems, or suicidal thoughts or behavior

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking clonazepam orally disintegrating tablets with certain other medicines can cause side effects or

affect how well clonazepam orally disintegrating tablets or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take clonazepam orally disintegrating tablets?

· Take clonazepam orally disintegrating tablets exactly as your healthcare provider tells you. Clonazepam is available as a tablet or as an orally disintegrating tablet.

· Do not stop taking clonazepam orally disintegrating tablets without first talking to your healthcare provider. Stopping clonazepam orally disintegrating tablets suddenly can cause serious problems.

· Clonazepam orally disintegrating tablets can be taken with or without water.

- Do not open the carton until you are ready to take clonazepam orally disintegrating tablets.
- After opening the carton, peel back the foil on the blister pack.
- Do not push the orally disintegrating tablet through the foil.
- After opening the blister pack, with dry hands, take the orally disintegrating tablet and place it in your mouth.
- The orally disintegrating tablet will melt quickly.

· If you take too much clonazepam orally disintegrating tablets, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking clonazepam orally disintegrating tablets?

· Clonazepam orally disintegrating tablets can slow your thinking and motor skills. Do not drive, operate heavy machinery, or do other dangerous activities until you know how clonazepam orally disintegrating tablets affects you.

· Do not drink alcohol or take other medicines that may make you sleepy or dizzy while taking clonazepam orally disintegrating tablets until you talk to your healthcare provider. When taken with alcohol or medicines that cause sleepiness or dizziness, clonazepam orally disintegrating tablets may make your sleepiness or dizziness much worse.

What are the possible side effects of clonazepam orally disintegrating tablets?

See "What is the most important information I should know about clonazepam orally disintegrating tablets?"

Clonazepam orally disintegrating tablets can also make your seizures happen more often or make them worse. Call your healthcare provider right away if your seizures get worse while taking clonazepam orally disintegrating tablets.

The most common side effects of clonazepam orally disintegrating tablets include:

· drowsiness	· dizziness	· fatigue
· problems with walking and coordination	· depression	· problems with memory

These are not all the possible side effects of clonazepam orally disintegrating tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store clonazepam orally disintegrating tablets?

- Store clonazepam orally disintegrating tablets between 59°F to 86°F (15°C to 30°C)
- **Keep clonazepam orally disintegrating tablets and all medicines out of the reach of children**

General Information about the safe and effective use of clonazepam orally disintegrating tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use clonazepam orally disintegrating tablets for a condition for which it was not prescribed. Do not give clonazepam orally disintegrating tablets to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about clonazepam orally disintegrating tablets that is written for health professionals.

What are the ingredients in clonazepam orally disintegrating tablets?

Active ingredient: clonazepam

Inactive ingredients: sorbitol, aspartame, sodium lauryl sulfate, crospovidone, mannitol, colloidal silicon dioxide, talc and magnesium stearate

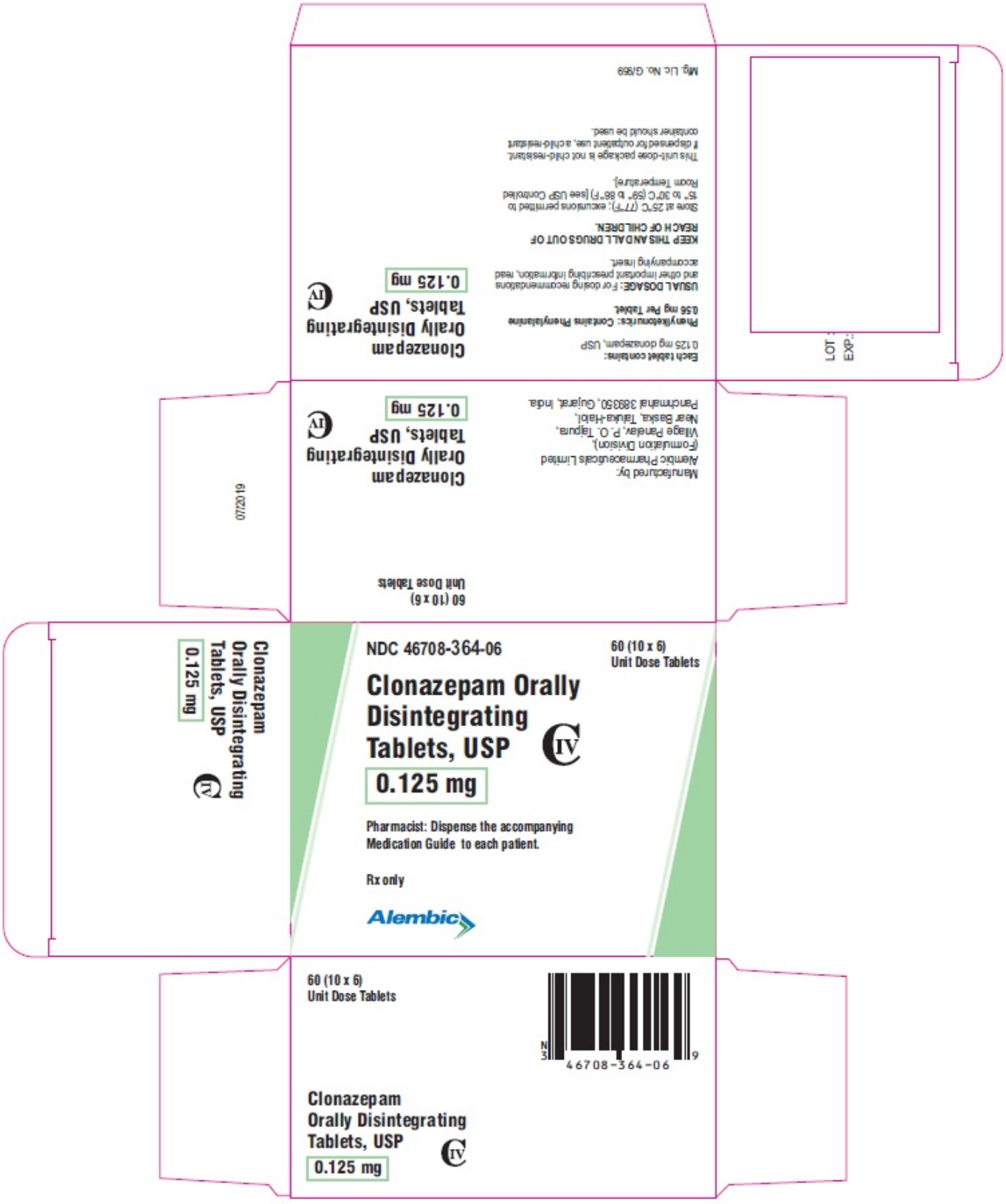
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Alembic Pharmaceuticals Limited
(Formulation Division),
Village Panelav, P. O. Tajpura,
Near Baska, Taluka-Halol,
Panchmahal 389350, Gujarat, India.

Revised: 12/2018

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL -0.125 mg

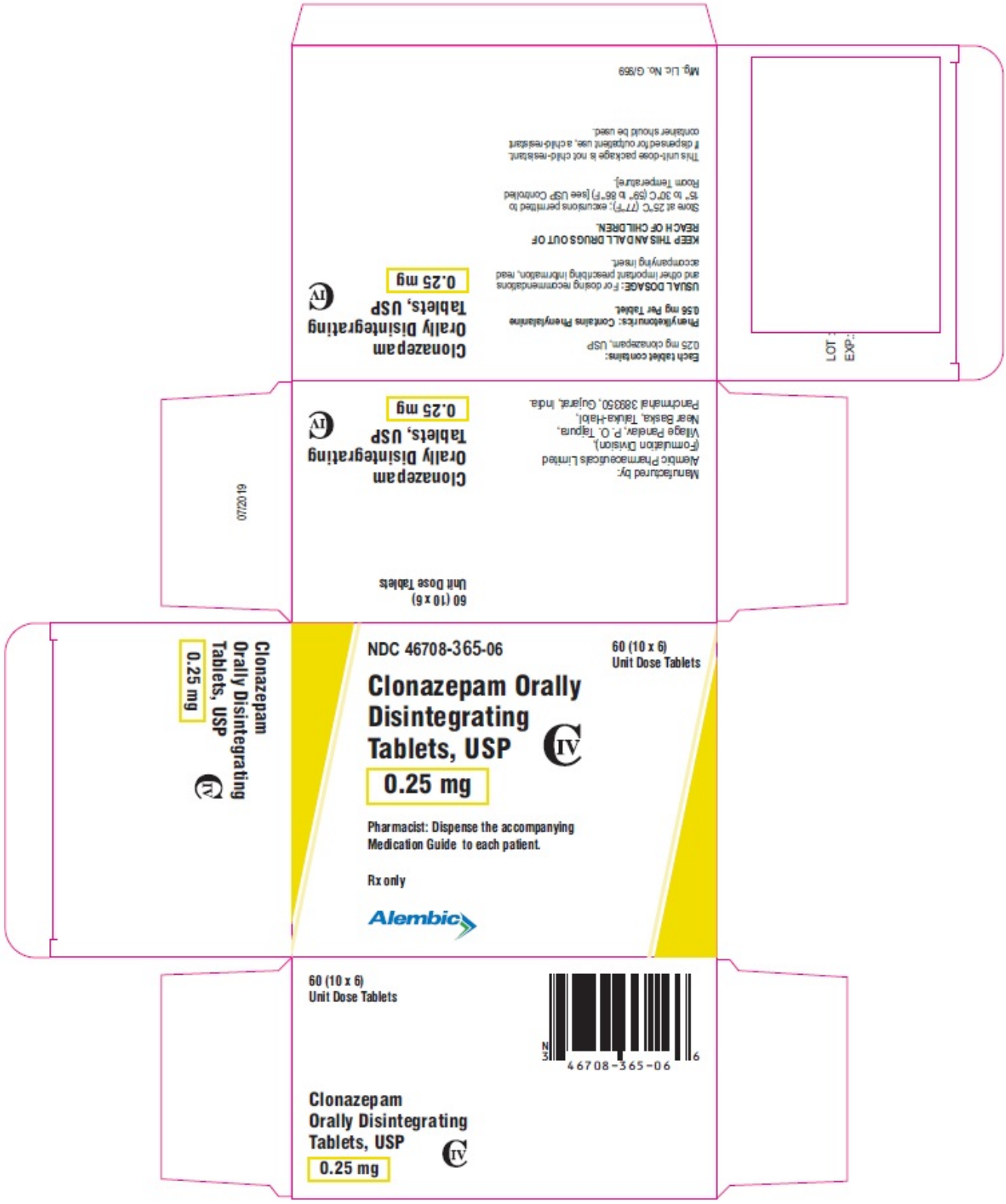
NDC 46708-364-06
Clonazepam Orally Disintegrating
Tablets, USP
0.125 mg
Pharmacist: Dispense the accompanying
Medication Guide to each patient.
Rx only
60 (10 x 6) Unit Dose Tablets
Alembic



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL -0.25 mg

NDC 46708-365-06

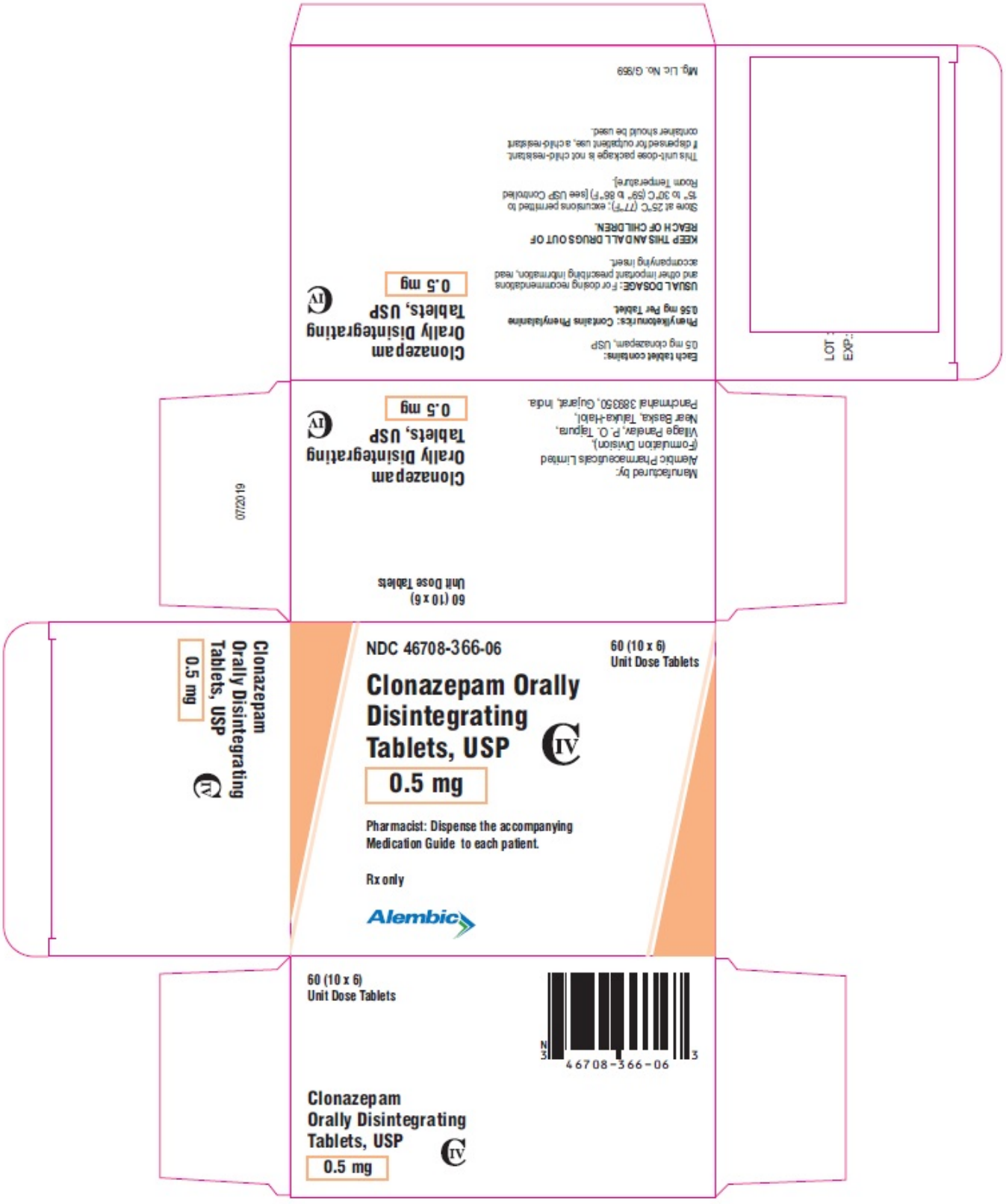
Clonazepam Orally Disintegrating Tablets, USP
0.25 mg
Pharmacist: Dispense the accompanying Medication Guide to each patient.
Rx only
60 (10 x 6) Unit Dose Tablets
Alembic



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL -0.5 mg

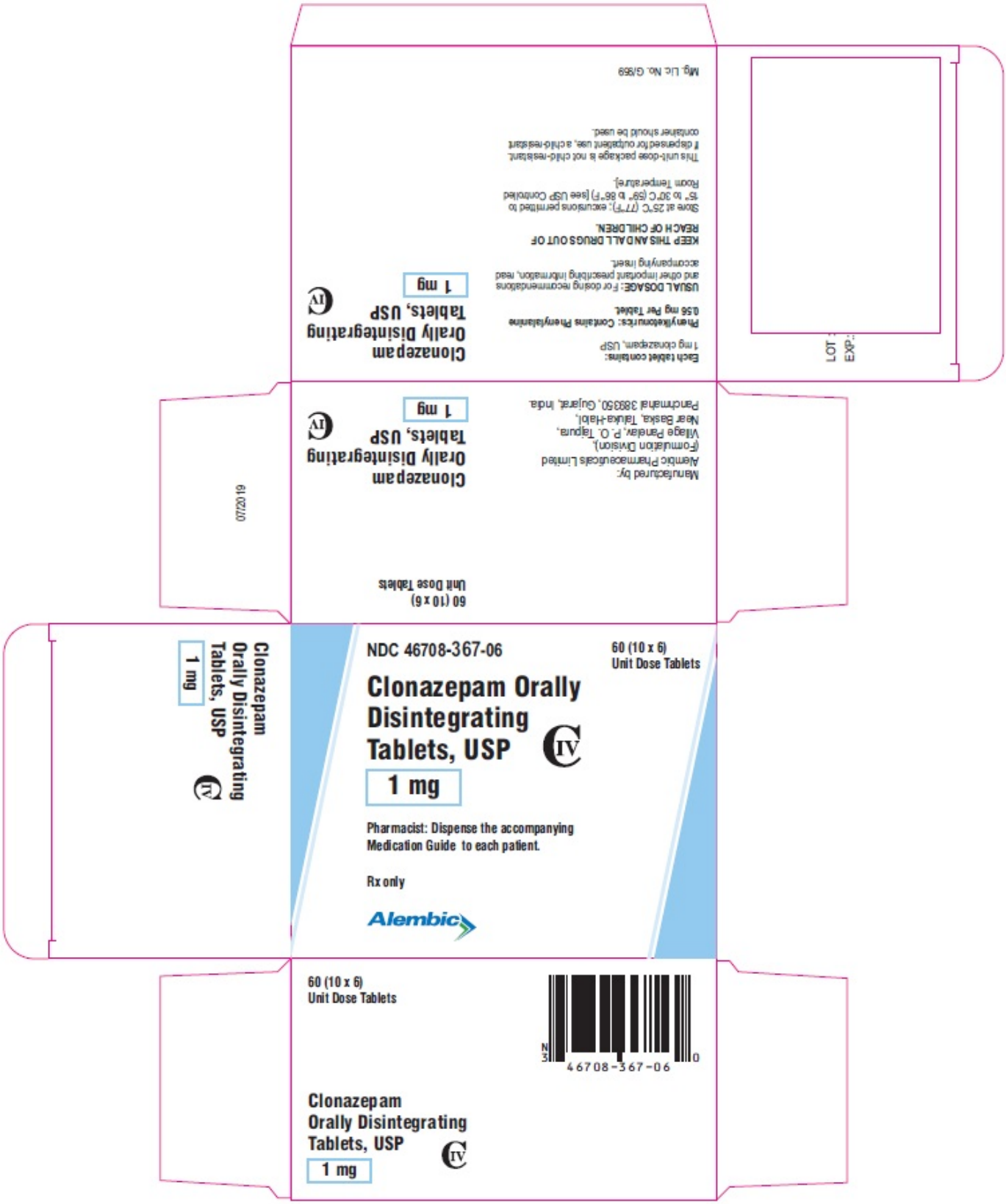
NDC 46708-366-06
Clonazepam Orally Disintegrating
Tablets, USP
0.5 mg
Pharmacist: Dispense the accompanying
Medication Guide to each patient.

Rx only
60 (10 x 6) Unit Dose Tablets
Alembic



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL -1 mg

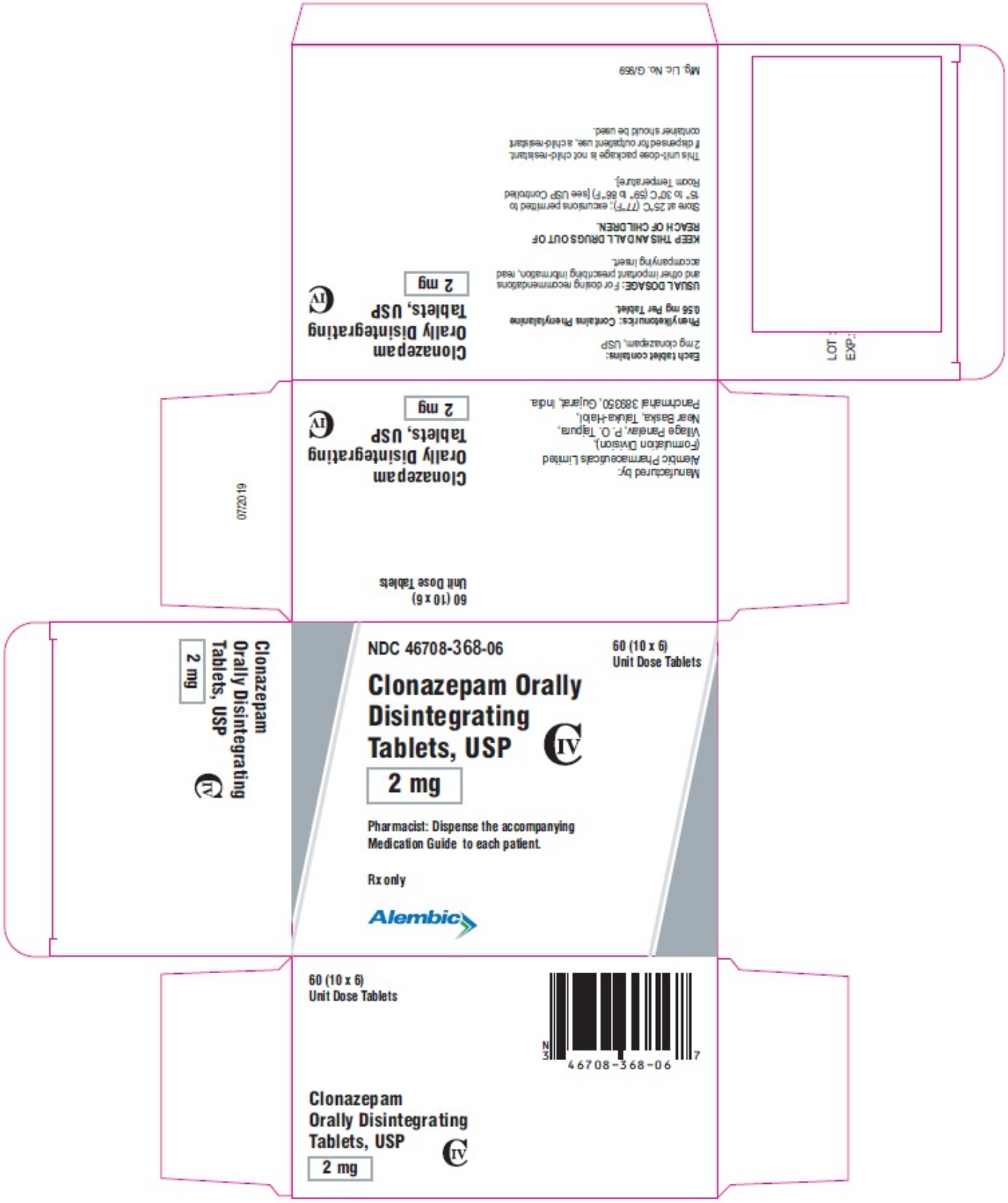
NDC 46708-367-06
Clonazepam Orally Disintegrating Tablets, USP
1 mg
Pharmacist: Dispense the accompanying Medication Guide to each patient.
Rx only
60 (10 x 6) Unit Dose Tablets
Alembic



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL -2 mg

NDC 46708-368-06
Clonazepam Orally Disintegrating
Tablets, USP
2 mg

Pharmacist: Dispense the accompanying Medication Guide to each patient.
Rx only
60 (10 x 6) Unit Dose Tablets
Alembic



CLONAZEPAM

clonazepam tablet, orally disintegrating

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-364
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CLONAZEPAM (UNII: 5PE9FDE8GB) (CLONAZEPAM - UNII:5PE9FDE8GB)	CLONAZEPAM	0.125 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SORBITOL (UNII: 506T60A25R)	
ASPARTAME (UNII: Z0H242BBR1)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
CROSPOVIDONE (UNII: 2S7830E561)	
MANNITOL (UNII: 3OWL53L36A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE (white to off white)	**Score**	no score
Shape	ROUND (flat-faced, beveled edge)	**Size**	6mm
Flavor		**Imprint Code**	L;523
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:46708-364-06	60 in 1 CARTON	07/01/2019	
1		6 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211033	07/01/2019	

CLONAZEPAM

clonazepam tablet, orally disintegrating

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-365
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CLONAZEPAM (UNII: 5PE9FDE8GB) (CLONAZEPAM - UNII:5PE9FDE8GB)	CLONAZEPAM	0.25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SORBITOL (UNII: 506T60A25R)	
ASPARTAME (UNII: Z0H242BBR1)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
CROSPOVIDONE (UNII: 2S7830E561)	
MANNITOL (UNII: 3OWL53L36A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE (white to off white)	**Score**	no score
Shape	ROUND (flat-faced, beveled edge)	**Size**	6mm
Flavor		**Imprint Code**	L;524
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:46708-365-06	60 in 1 CARTON	07/01/2019	
1		6 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211033	07/01/2019	

CLONAZEPAM

clonazepam tablet, orally disintegrating

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-366

Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CLONAZEPAM (UNII: 5PE9FDE8GB) (CLONAZEPAM - UNII:5PE9FDE8GB)	CLONAZEPAM	0.5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SORBITOL (UNII: 506T60A25R)	
ASPARTAME (UNII: Z0H242BBR1)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
CROSPOVIDONE (UNII: 2S7830E561)	
MANNITOL (UNII: 3OWL53L36A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE (white to off white)	**Score**	no score
Shape	ROUND (flat-faced, beveled edge)	**Size**	6mm
Flavor		**Imprint Code**	L;525
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:46708-366-06	60 in 1 CARTON	07/01/2019	
1		6 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211033	07/01/2019	

CLONAZEPAM

clonazepam tablet, orally disintegrating

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-367
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CLONAZEPAM (UNII: 5PE9FDE8GB) (CLONAZEPAM - UNII:5PE9FDE8GB)	CLONAZEPAM	1 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SORBITOL (UNII: 506T60A25R)	
ASPARTAME (UNII: Z0H242BBR1)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
CROSPOVIDONE (UNII: 2S7830E561)	
MANNITOL (UNII: 3OWL53L36A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE (white to off white)	**Score**	no score
Shape	ROUND (flat-faced, beveled edge)	**Size**	6mm
Flavor		**Imprint Code**	L;526
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:46708-367-06	60 in 1 CARTON	07/01/2019	
1		6 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211033	07/01/2019	

CLONAZEPAM

clonazepam tablet, orally disintegrating

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-368
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CLONAZEPAM (UNII: 5PE9FDE8GB) (CLONAZEPAM - UNII:5PE9FDE8GB)	CLONAZEPAM	2 mg

Inactive Ingredients	
Ingredient Name	Strength
SORBITOL (UNII: 506T60A25R)	
ASPARTAME (UNII: Z0H242BBR1)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
CROSPOVIDONE (UNII: 2S7830E561)	
MANNITOL (UNII: 3OWL53L36A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE (white to off white)	**Score**	no score
Shape	ROUND (flat-faced, beveled edge)	**Size**	6mm
Flavor		**Imprint Code**	L;527
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-368-06	60 in 1 CARTON	07/01/2019	
1		6 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211033	07/01/2019	

Labeler - Alembic Pharmaceuticals Limited (650574663)

Establishment

Name	Address	ID/FEI	Business Operations
Alembic Pharmaceuticals Limited		650574671	MANUFACTURE(46708-364, 46708-365, 46708-366, 46708-367, 46708-368)

Revised: 7/2019 Alembic Pharmaceuticals Limited